Impact of age at type 2 diabetes mellitus diagnosis on mortality and vascular complications

Impact of age at type 2 diabetes mellitus diagnosis on mortality and vascular complications: systematic review and meta-analyses

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ABSTRACT

Aims/hypothesis: Few studies examine the association between age at diagnosis and subsequent complications from type 2 diabetes. This paper aims summarise the risk of mortality, macrovascular and microvascular complications associated with age at diagnosis of type 2 diabetes.

Methods: Data were sourced from Medline and All EBM (Evidence Based Medicine) databases from inception to July 2018. Observational studies, investigating the effect of age at diabetes diagnosis on macrovascular and microvascular diabetes complications in adults with type 2 diabetes were selected according to pre-specified criteria. Two investigators independently extracted data and evaluated all studies. If data were not reported in a comparable format, data were obtained from authors, presented as minimally adjusted odds ratios (and 95% confidence intervals) per one year increase in age at diabetes diagnosis, adjusted for current age for each outcome of interest. The study protocol was recorded with PROSPERO International prospective register of systematic reviews (CRD42016043593).

Results: Data from 26 observational studies comprising 844 081 individuals from 30 countries were included. Random effects meta-analyses with inverse variance weighting were used to obtain the pooled odds ratios. Age at diabetes diagnosis was inversely associated with risk of all-cause mortality, macrovascular and microvascular disease (all $p<0.001$). Each one-year increase in age at diabetes diagnosis was associated with a 4, 3 and 5% decreased risk of all-cause mortality, macrovascular disease and microvascular disease respectively, adjusted for current age. The effects were consistent for the individual components of the composite outcomes (all $p<0.001$).

Conclusions/interpretation: Younger rather than older, age at diabetes diagnosis was associated with higher risk of mortality and vascular disease. Early and sustained interventions to delay type 2 diabetes onset and improve glycaemia and cardiovascular risk profiles of those already diagnosed are essential to reduce morbidity and mortality.

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RESEARCH IN CONTEXT

What is already known about this subject? (maximum of 3 bullet points)

- Type 2 diabetes, conventionally considered a disease of middle and older age, is increasingly diagnosed at a younger age.
- Despite this, the pathogenesis of the long-term vascular complications associated with early or late onset type 2 diabetes is not well characterised.
- Although there are several studies examining the relationship between age at diabetes diagnosis and long-term complications among people with type 2 diabetes. These studies have varied widely in population characteristics or methodological rigour, and report inconsistent findings with some suggesting that younger age at diabetes diagnosis is associated with increased risk of complications, decreased risk of complications, no difference in risk of complications or variable effects in different end organs.

What is the key question? (one bullet point only; formatted as a question)

- What is the risk of mortality, macrovascular and microvascular complications associated with age at diagnosis of type 2 diabetes mellitus.

What are the new findings? (maximum of 3 bullet points)

- This analysis integrates data from over half a million people with diabetes worldwide to evaluate the risk of a range of diabetes complications with respect to age at diagnosis.
- Each one-year increase in age at diabetes diagnosis was associated with a 4, 3 and 5 % decreased risk of all-cause mortality, macrovascular disease and microvascular disease, respectively.
- Further research is needed on how to optimise the cardiovascular risk profiles and trajectories of younger as well as older patients with diabetes

How might this impact on clinical practice in the foreseeable future? (one bullet point only)

- Identification and quantification of the higher risk of mortality and vascular disease conferred by younger age at type 2 diabetes diagnosis may enable risk stratification of people early in the condition and provide greater opportunities for interventions to reduce risk of adverse outcomes.

INTRODUCTION

The International Diabetes Federation estimates that the prevalence of diabetes will rise from 425 million people worldwide in 2017, to 629 million by 2045 [1]. Type 2 diabetes, conventionally considered a disease of middle and older age, is increasingly diagnosed at a younger age [1, 2]. Type 2 diabetes and its associated complications contribute to 8.4% of deaths worldwide, consuming significant healthcare resources [3]; this is likely to rise exponentially given the increasing prevalence of the condition [1].

Despite significant diagnostic, monitoring and treatment advances, type 2 diabetes remains associated with increased mortality and morbidity compared with the general population [4]. However, the pathogenesis of the long-term vascular complications associated with early or late onset type 2 diabetes is not well characterised, and although the mechanisms for the development of complications maybe similar [5], recent evidence suggests an accelerated course in people diagnosed with early onset type 2 diabetes [6, 7]. Proposed mechanisms include a longer lifetime exposure to the adverse diabetic milieu and/or early onset type 2 diabetes representing an inherently more aggressive metabolic phenotype with rapid onset of β-cell failure and insulin resistance compared to late onset disease [2, 8, 9]. Novel cluster analyses raise the possibility of type 2 diabetes representing a clustering of up to five disease subgroups with distinct age at diagnosis, genetics, mechanisms of disease progression and risk of diabetic complications [10]. Of the five groups identified, the ‘mild age-related diabetes’ subgroup contained elderly people who experienced the most benign disease course compared with the ‘mild obesity-related diabetes’ group, characterised by younger age at onset and obesity.

There are several studies examining the relationship between age at diabetes diagnosis and long-term complications among people with type 2 diabetes. These studies have varied widely in population characteristics or methodological rigour, and report inconsistent findings with some suggesting that younger age at diabetes diagnosis is associated with increased risk of complications [6, 7, 11-15], decreased risk of complications [16, 17], no difference in risk of complications [18] or variable effects in different end organs [19, 20]. Additionally, some studies have proposed that longer diabetes duration [21, 22] or more adverse cardiovascular risk profiles [23, 24] underlie the greater risk of development of vascular complications associated with type 2 diabetes diagnosed at a younger age, whilst other studies have suggested that impact of age at diagnosis may vary with ethnicity [25].

Evidence of a clinically meaningful effect of age at diagnosis of type 2 diabetes beyond the ageing process itself would have substantial implications for diabetes prevention, treatment and the development and implementation of cardiovascular risk prediction tools. The aim of our study was thus to examine the effect of age at diagnosis of type 2 diabetes on risks of complications, focusing on all-cause mortality, macrovascular events and microvascular events.

METHODS

Data Sources and Searches

A systematic search of published literature was conducted in Medline and All EBM (Evidence Based Medicine) databases (including Cochrane Database of Systematic Reviews, ACP Journal Club Database of Abstracts of Reviews of Effects, Cochrane Central Register of Controlled Trials, Cochrane Methodology Register, Health Technology Assessment and NHS Economic Evaluation Database) using the subject headings and key terms detailed in Appendix 1. The study methods and reporting follow the Meta-analyses Of Observational Studies in Epidemiology (MOOSE) and Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) guidelines [26, 27]. The study protocol was recorded with PROSPERO International prospective register of systematic reviews (CRD42016043593). The search was limited to humans and English language articles and was initially conducted in July 2016 with no time restrictions and updated in July 2018.

Study selection

The inclusion criteria were determined *a priori* (Appendix 1). To be included, studies had to meet the following criteria: be a study of adult participants with type 2 diabetes, investigating the effect of age at diabetes diagnosis on macrovascular and microvascular diabetes complications. The study had to assess one or more of the following outcome variables (all-cause mortality, macrovascular disease, microvascular disease, retinopathy, nephropathy, neuropathy, cardiovascular disease, cerebrovascular disease and peripheral vascular disease) and have an available mortality/complication rate, where mortality was either a pre-specified primary or secondary outcome, or the methods indicated complete follow-up of participants.

Two independent authors (NN and AG) assessed the title and abstracts of retrieved records for relevance and duplication. Authors then reviewed the full text of potentially eligible

citations to identify studies that fulfilled the inclusion criteria. Any uncertainties regarding study inclusion and data extraction were discussed with an experienced systematic reviewer (AC), statistician (SH) and senior clinician (SZ). The references cited in the retrieved publications were screened for potentially eligible studies. When several articles from the same study had reported on the same endpoint, only the data representing the longest follow-up were extracted.

Data extraction and quality assessment

Data were extracted from included studies using a specially developed data extraction form. Information was obtained regarding study design and location, participant characteristics, outcome variables and results. Given the wide variation in data reporting and adjustment for confounders, meaningful interpretation, comparison and meta-analysis was not possible. Therefore, we contacted authors to reanalyse and present data in a homogeneous format to enable data pooling and comparison. Corresponding authors were contacted by email at least twice (if data were not reported in a suitable format) to request data, presented as minimally adjusted odds ratios [odds ratio (OR) 95% confidence interval (CI)] per one year increase in age at diabetes diagnosis, with adjustment for current age (or diabetes duration) for each outcome of interest. This format was chosen as the majority of studies presented the results in this way.

Risk of bias of included studies was assessed using a specially developed data extraction form, based on the Newcastle–Ottawa Scaling for non-randomized studies [28, 29]. Quality assessment criteria included representativeness of participants, validity of the diagnostic criteria, determination of age at diagnosis, outcome assessment, withdrawals and losses to follow-up. Each study was then allocated a risk of bias rating (Appendix 3).

Exposures

Current age was reported by each study as age at entry into the study or age at baseline assessment. Age at type 2 diabetes diagnosis was reported as the age of the people at the diagnosis of type 2 diabetes with diabetes duration reported or calculated as current age minus age at diabetes diagnosis.

Outcomes

The primary *a priori* outcomes were all-cause mortality, macrovascular disease (composite of coronary heart disease, cerebrovascular disease and peripheral vascular disease) or microvascular disease (composite of retinopathy, nephropathy and neuropathy). The secondary *a priori* outcomes were retinopathy, nephropathy, neuropathy, coronary heart disease, cerebrovascular disease and peripheral vascular disease.

Statistical analysis

Interdependence of current age, age at diabetes diagnosis and diabetes duration precluded use of all 3 variables in the same model; hence the use of models containing either age at diabetes diagnosis adjusted for current age or age at diabetes diagnosis adjusted for diabetes duration. Adjustment for current age was to remove the effect of aging *per se*. Adjustment for diabetes duration was to remove the effect of the time-point at which observations happened to be made in the course of illness for each individual; an individual observed early in their illness would appear to have a longer time to develop complications than the same individual observed late in their illness. For studies reporting in multiple models, we extracted data for both minimally adjusted and maximally adjusted increased risk estimates. Unless otherwise stated, the least adjusted risk estimates from each study were used, provided diabetes duration was included. Review Manager (RevMan) software Version 5.3 was used for all statistical analyses [30].

Data were combined in meta-analyses to calculate pooled risk estimates presented as odds ratios (OR) and 95% Confidence Interval (CI) of the effect of age at diabetes diagnosis (per year) adjusted for current age (or diabetes duration – supplemental analyses), on outcomes using both fixed and random-effects models (generic inverse variance method) [31]. There were no significant differences between fixed- and random-effects analyses. Random effects models are presented given heterogeneity among the studies [32]. Crude data were included where possible, given variable control for confounding factors. However, some articles presented adjusted ORs only.

I^2 was used to assess heterogeneity with values of 25%, 50%, and 75% considered low, moderate and high, respectively [33]. Funnel plots were used to explore potential publication bias [34, 35]. A scatter plot of the t-statistic associated with each study estimate value assessed the contribution of each study to the study-estimate random effect versus the log of the SE (standard error) of the effect.

RESULTS

Characteristics of included studies

Electronic database and reference searching yielded 2219 publications, of which 156 were reviewed in full-text (Figure 1). Of 34 eligible studies, 26 studies comprising 844 081 individuals were included and 8 were excluded because data were not provided in the required format in the publication and attempts to contact authors were not successful. The 25 included studies were either cross-sectional (13 studies) or cohort (13 studies) in design. The updated search in 2018 enabled the inclusion of data from 3 studies. The mean age of study participants ranged from 21.6 to 67.4 years. The proportion of female study participants ranged from 42.5% to 68.6%. Table 1 summarises the characteristics of the included studies which comprise 844 081 participants from 30 countries worldwide.

PRIMARY OUTCOMES

Effects of age at diabetes diagnosis adjusted for current age on all-cause mortality, macrovascular disease and microvascular disease

For all-cause mortality, data from 5 studies [20, 21, 25, 36, 37], comprising 844 081 participants indicated that each one year increase in age at diabetes diagnosis was associated with a 4% decreased risk of all-cause mortality (OR 0.96 [0.94, 0.98], p<0.001) when adjusted for current age. For macrovascular disease, data from 8 studies [20, 23-25, 37-40], comprising 356 008 participants indicated that each one year increase in age at diabetes diagnosis was associated with a 3% decreased risk of macrovascular disease (OR 0.97 [0.96, 0.98], p<0.001) when adjusted for current age. For microvascular disease, data from 8 studies [20, 24, 25, 38-42] comprising 147 502 participants indicated that each one year increase in age at diabetes diagnosis was associated with a 5% decreased risk of microvascular disease (OR 0.95 [0.94, 0.96], p<0.001) when adjusted for current age. Significant heterogeneity in the magnitude of the effects was evident between studies for these outcomes (all Chi^2 p=<0.001, all $I^2 \geq 93$ %) (Figure 2).

SECONDARY OUTCOMES

Effects of age at diabetes diagnosis adjusted for current age on coronary heart disease, cerebrovascular disease, peripheral vascular disease, retinopathy, nephropathy and neuropathy)

Data for individual vascular complications were available from 13 studies, comprising 356 038 participants and adjusted for current age. Each one year increase in age at diabetes diagnosis was associated with a 2% decreased risk of coronary heart disease (OR 0.98

[0.97, 0.98], p<0.001), a 2% decreased risk of cerebrovascular disease (OR 0.98 [0.97, 0.99], p<0.001) and a 3% decreased risk of peripheral vascular disease (OR 0.97 [0.96, 0.99], p<0.001). Each one year increase in age at diabetes diagnosis was associated with an 8% decreased risk of retinopathy (OR 0.92 [0.90, 0.95], p<0.001), a 6% decreased risk of nephropathy (OR 0.94 [0.92, 0.96], p<0.001) and a 5% decreased risk of neuropathy (OR 0.95 [0.94, 0.96], p<0.001) (Figure 3). Significant heterogeneity in the magnitude of the effects was evident between studies for these outcomes (all Chi^2 p= <0.001, all $I^2 \geq 48\%$).

SENSITIVITY ANALYSES

Effects of age at diabetes diagnosis adjusted for diabetes duration on all-cause mortality, macrovascular disease and microvascular disease

Data for these analyses were obtained from ten studies comprising 390 139 participants and adjusted for diabetes duration (ESM figure 1). Each one year increase in age at diabetes diagnosis was associated with a 6% increased risk of all-cause mortality (OR 1.06 [1.03, 1.09], p<0.001), a 6% increased risk of macrovascular disease (OR 1.06 [1.04, 1.07], p<0.001) and a 5% increased risk of microvascular disease (OR 1.05 [1.02, 1.08], p<0.001).

Methodological quality

Risk of bias assessment of the included studies is presented in Appendix 3. Study participants were recruited to randomised clinical trials or selected from large clinical datasets. Inclusion and exclusion criteria were adequately described in all studies. Of the included studies 24 [14, 15, 20, 21, 23-25, 36-52] were of high quality and 2 [53, 54] of medium quality due to insufficient adjustment of confounding variables. In addition, 24 studies [14, 15, 20, 21, 23-25, 36-52] demonstrated low risk of bias and 2 [53, 54] demonstrated a moderate risk of bias due to insufficient adjustment for confounding variables (confounding bias) (ESM table 3). Funnel plots did not suggest the presence of publication bias (ESM figure 2).

CONCLUSIONS

This comprehensive systematic review and meta-analysis compiles the results of 25 studies investigating the effects of age at diabetes diagnosis on mortality and subsequent complications in 844 081 participants with type 2 diabetes from diverse populations across the Asia Pacific, Europe and North America. We report an inverse relationship between age at diabetes diagnosis and risk of major diabetes complications after adjustment for current

age. Each one-year increase in age at diabetes diagnosis was associated with a 4, 3 and 5% decreased risk of all-cause mortality, macrovascular disease and microvascular disease respectively. These effects were consistent across the individual components of the composite outcomes (coronary heart disease, cerebrovascular disease, peripheral vascular disease, retinopathy, nephropathy and neuropathy) and reversed when the models included diabetes duration rather than current age.

While prior studies have assessed the effects of age at diabetes diagnosis on diabetes complications, to our knowledge, this is the first systematic review and meta-analysis exploring associations between age at diabetes diagnosis and subsequent outcomes. Interdependence of current age, age at diabetes diagnosis and diabetes duration precluded investigation of all 3 variables simultaneously; hence the use of models containing either age at diabetes diagnosis adjusted for current age or age at diabetes diagnosis adjusted for diabetes duration. Those diagnosed with diabetes at older age may be more likely to have accumulated adverse cardiovascular risk factors compared with those diagnosed at a younger age. Since advancing age is a powerful predictor of vascular complications, for the same diabetes duration, people with younger age at diagnosis are likely to have lower absolute risks of events as compared to people with older age at diagnosis. Over time however, the effects of both aging and disease duration may be amplified resulting in premature complications and death in people diagnosed with type 2 diabetes at a younger age. For example a person diagnosed with type 2 diabetes at age 30 years would have a lower absolute risk of complications compared with another person diagnosed age 50 years, however by the time they both reach 60 years, the person diagnosed at a younger age would have a higher relative and absolute risk due to the effects of ageing, compounded by the effects of longer diabetes duration. This pattern has been observed in several young onset type 2 diabetes populations [21, 55]. Thus, younger people pose a significant challenge for clinicians and decision makers who need to be aware of these compounding pathologies of natural ageing and premature vascular aging associated with type 2 diabetes. Further, people diagnosed at a younger age still have the potential to develop type 2 diabetes complications at an earlier stage of life age, at a time when they are more likely to cause greater disability and loss of productivity compared with people diagnosed at an older age.

There are lack of RCT studies on achieving good glycaemic control and optimisation of cardiovascular risk factors in young-onset type 2 diabetes, as many of these trials recruited

middle-aged people with long disease duration at greatest absolute risk of complications. However, data from these older populations may not reflect the pathophysiology of type 2 diabetes in younger people, given evidence suggesting that younger and older patients may differ in the development of diabetes complications. Further, many of these studies lack sufficient follow up to capture complications in younger people who may have a longer time to event. The observations of this study and others examining type 2 diabetes complications [15, 23, 38, 51] add impetus to conducting trials examining this young cohort. There is an urgent need for data specifically pertaining to younger type 2 diabetes populations examining the trajectory of vascular complications and the impact of interventions (pharmacological as well as non-pharmacological approaches) to improve outcomes.

We found that age at diabetes diagnosis adjusted for current age was inversely associated with risk of all-cause death, macrovascular and microvascular disease. Our findings underscore the importance of cardiovascular risk management among people with diabetes. Screening for and prevention of macrovascular complications is particularly important for older people with diabetes who have the highest short-term absolute risk. Increasing age remains one of the most important risk factors for the development of macrovascular complications. However, it is also important to note that people diagnosed with diabetes at a younger age have longer lifetime risk of developing significant complications, thus achieving good glycaemic control and optimisation of cardiovascular risk factors is of particular importance across their lifespan. This difference in risk between younger and older people in terms of absolute vs lifetime risks of type 2 diabetes complications, should perhaps be recognised in diabetes management guidelines with increased promotion of screening programs in older people with type 2 diabetes and a greater emphasis on preventive measures for younger patients with type 2 diabetes.

As early intensive multifactorial risk factor intervention is important for the prevention of long term macrovascular complications among people with newly diagnosed diabetes [56], our findings further suggest that this should be sustained long-term to minimise risks over time. Clearly, strategies are needed to ensure sustained adherence to lifestyle behaviours and therapies proven to have cardiovascular benefits among people with diabetes. Existing treatment guidelines are limited by being reactive to suboptimal glycaemic control after it has developed, but do not have means to predict which people require intensified treatment. Refined stratification using age at diagnosis, may provide a method of identifying at diagnosis those at greatest risk of complications who would most benefit from targeted,

individualised treatment regimens. Moreover, public health measures to delay and/or prevent the onset of type 2 diabetes to older age may yield benefits by reducing the duration of diabetes and burden of complications.

The development and progression of type 2 diabetes represents a complex interplay between genetic, epi-genetic, lifestyle, demographic, socio-economic, therapeutic and environmental factors. Given the myriad factors involved, and the variable reporting across included studies, it was difficult to establish uniformity in study definitions and co-variate adjustment across studies. There was considerable variation in the definitions of “younger” and “older” age at type 2 diabetes diagnosis, with some studies defining “younger” as less than 30 years of age, less than 40 years or less than 50 years of age. To mitigate this, we examined the effect of age at diabetes diagnosis (adjusted for current age), in yearly increments. Studies varied greatly with respect to measured confounding factors such as ethnicity, study country and year, type 2 diabetes diagnostic criteria, medication use, glycaemic control age, obesity, cardio-metabolic risk factors, co-morbid conditions, recruitment, source of participants, family history, healthcare access and sociodemographic factors. We were unable to adjust for these factors, as this data was either unavailable or not comparable due to the lack of standardised definitions across published studies. Moving forward, standardised approaches to reporting and complete data capture of relevant variables will assist with pooling and analysis of disparate datasets. This may be facilitated by the creation of international data registries. Performance bias (a potential difference in the care provided between early and later onset type 2 diabetes groups and between different centres) could not be assessed. Older people with type 2 diabetes may have cognitive impairment or other comorbidities precluding treatment intensification or even leading to de-intensification. Alternatively, people diagnosed with type 2 diabetes at a younger age may have been treated more intensively than people diagnosed at an older age. If this were the case, this bias would ameliorate the differences between groups, such that our data may actually underestimate the true extent of the effect of younger age at type 2 diabetes diagnosis. However, this would seem less likely as several studies suggest that younger people with type 2 diabetes have poorer glycaemic control, lower adherence to therapy and inferior self-care practices compared with older people [57, 58]. In fact, the data suggests that younger people with type 2 diabetes may receive suboptimal medical attention was given to younger patients, potentially due in part, to an absence of clinical guidelines targeted to younger people with type 2 diabetes and possibly the underestimation of risks of complications in these patients [38].

The strength of this meta-analysis is the extensive and comprehensive literature search and focus on studies examining younger and older people with type 2 diabetes. Six databases were searched, a risk of bias appraisal performed, and reanalyses were undertaken, enabling inclusion of data from more than half a million people with type 2 diabetes worldwide. Collaboration with other authors facilitated more homogeneous data definitions, data integration, and meta-analyses. We found that there was high concordance between the different studies in the meta-analyses, such that the direction of the effects were consistent, although the magnitude of effects and the confidence intervals varied. This may be due to differences in study size, however contributions from genetic, ethnic and healthcare variations in study populations cannot be excluded. Nevertheless, the direction of the effects was consistent across the studies from different countries.

As with many systematic reviews and meta-analyses, this meta-analysis has some limitations. Not all identified studies were included in the meta-analyses due to difficulties sourcing comparable data from authors. The inability to acquire data from all eligible studies is not unexpected and is a part of the meta-analysis process [59]. We based our classification of age at type 2 diabetes diagnosis on the definitions used in each individual study, even though these definitions may have differed. It would be impossible to apply retrospectively a single definition of age at diagnosis to a large number of samples characterised with different variables in different studies. Additionally, the criteria for the diagnosis and classification of type 2 diabetes have changed with the advent of new technologies such as the determination of pancreatic auto-antibodies and C-peptide levels, as have the methods used to differentiate type 2 from other forms of diabetes (principally type 1 and monogenic diabetes). Lastly, due in part to the nature of the study question, the included studies were observational in design and therefore subject to potential the biases (confounding and selection) inherent to analyses of observational data. However, meta-analyses of observational studies can provide valuable insights, especially when randomised clinical trials are unavailable or inappropriate to address the question [34] as is the case here. Findings from this review are based on observational data and therefore causality may not be attributed. Thus, although these findings may be applicable on a population level, any recommendations need to be individualised to the clinical situation of each person with type 2 diabetes.

We have completed the first systematic review and meta-analysis examining the effects of age at type 2 diabetes diagnosis on all-cause mortality, microvascular and macrovascular

complications. This comprehensive analysis, comprising over half a million participants, indicates that when adjusted for current age, younger age at type 2 diabetes diagnosis is associated with increased risk of mortality, macrovascular and macrovascular complications. Identification and quantification of the increased risk of mortality and vascular disease conferred by younger age at type 2 diabetes diagnosis may enable risk stratification of people in early in the condition and thereby provide greater opportunities for interventions to reduce risk of complication-associated morbidity and mortality for this increasing population demographic developing type 2 diabetes.

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Authors' Contributions

Concept and design: Nanayakkara Gadowski Teede Curtis Zoungas

Data acquisition, analysis or interpretation: Nanayakkara, Curtis, Heritier, Gadowski, Pavkov, Kenealy, Owens, Thomas, Wong, Song, Chan, Luk, Penno, Ji, Magliano, Mohan, Anandakumar, Gasevic, Romero-Aroca, Chalmers, Zoungas

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The authors NN, AMG, SH and SZ had full access to the data and take responsibility for the integrity of the data and accuracy of the analysis. All authors have read and approved the final manuscript. We would like to acknowledge the assistance of Marie Misso and Elspeth Lilburn in completing this work.

Conflict of Interest Disclosure

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Disclaimer

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Data Sharing Statement

Application for datasets generated during and/or analysed during the current study may be considered by the corresponding author on reasonable request.

TABLES

Table 1: Characteristics of included studies

Study Authors	Year published	Study period	Country/ies	Sample size[a]	Mean age (y)	% Female	Study design	Outcomes
Amutha A., et al [41]	2017	2001-ongoing	India	198	21.6	42.7	Cohort	Retinopathy Neuropathy Nephropathy Peripheral Vascular Disease
Amutha A, Dutta et al [43]	2011	1992-2009	India	2630	28.2	NR	Cohort	Retinopathy Neuropathy Nephropathy
Cai, X., et al [14]	2014	2004 -2011	China	3 100	57.1	60.7	Cohort	Retinopathy
Chan, J.C., et al [38]	2014	1995 – 2009	China	9 506	57.4	53.8	Cohort	Macrovascular Disease Microvascular Disease Coronary Heart Disease Cerebrovascular Vascular Disease Peripheral Vascular Disease Retinopathy Nephropathy Neuropathy
Chen, M.S., et al [53]	1992	1985 – 1986	Taiwan	527	NR	55.0	Cross sectional	Retinopathy
Hamman, R.F., et al [54]	1989	1984 – 1986	USA	251	NR	NR	Cross sectional	Retinopathy
Huo, L., et al [52]	2018	1997-2011	Australia	743 709	60.2	46.0	Cohort	All-Cause Mortality
Huo, X., et al [37]	2016	2012	China	222 770	58.3	46.0	Cross sectional	Microvascular Macrovascular Disease Retinopathy Nephropathy
Kenealy, T., et al [25]	2008	2000–2005	New Zealand	67 563	60.5	51.0	Cohort	Macrovascular Disease Coronary Heart Disease Cerebrovascular Disease Peripheral Vascular Disease
Nanayakkara, N., et al [39]	2017	2015	Australia	3419	62.9	46.1	Cross sectional	Macrovascular Disease Microvascular Disease Coronary Heart Disease Theory Cerebrovascular Vascular Disease Retinopathy Nephropathy

Pavkov, M.E., et al [21]	2006	1965–2002	USA	3 653	40.9	61.9	Cohort	All-Cause Mortality Nephropathy
Pradeepa R, Rema M., et al [45]	2008	2001-ongoing	India	1629	50.4	55.4	Cross sectional	Neuropathy
Pradeepa R, Chella S., et al [44]	2014	2001-ongoing	India	1755	50.7	56.2	Cross sectional	Peripheral Vascular Disease
Pradeepa R, Anjana RM., et al [42]	2010	2001-ongoing	India	1608	NR	NR	Cross sectional	Microvascular Disease
Penno et al [36]	2018	2006-2008	Italy	15 773	66.6	43.1	Longitudinal	All-cause mortality
Pugliese, G., et al [40]	2012	2007 – 2008	Italy	15 933	66.2	43.7	Cross sectional	Macrovascular Disease Coronary Heart Disease Cerebrovascular Disease Retinopathy
Rema, M., et al [46]	2005	2001-ongoing	India	1715	52.0	55%	Cross sectional	Retinopathy
Romero-Aroca, P., et al [47]	2017	2007-2017	Spain	15 030	65.6	43.8	Longitudinal	Retinopathy Nephropathy
Song, S.H. and C.A. Hardisty [23]	2009	2008	UK	2 733	64.2	NR	Cross sectional	Macrovascular Disease Coronary Heart Disease Cerebrovascular Disease Peripheral Vascular Disease Neuropathy Retinopathy
Song, S.H. and T.A. Gray [48]	2011	NR	UK	2 516	63.1	NR	Cross sectional	Retinopathy
Thomas, R.L et al [49]	2015	2005 – 2009	UK	152 156[c]	67.4	68.6	Cohort	Retinopathy
Unnikrishnan, R. Anjana., et al [50]	2017	2005 – 2009	India	534	Younger onset – 31.6 Older onset – 69.9	NR	Cohort	Retinopathy Neuropathy Nephropathy Peripheral Vascular Disease
Unnikrishnan, RI, Rema M., et al [51]	2007	2005 – 2009	India	1716	50.7	55.2	Cross sectional	Nephropathy
Wong, J., et al [15]	2008	1989 – 2007	Australia	1 476	65.0[e]	44.6	Cohort	Retinopathy
Yeung, R.O., et al [24]	2014	2007 – 2012	Hong Kong, China, India, Philippines, South Korea, Vietnam,	42 453	57.5	47.0	Cross sectional	Retinopathy Neuropathy Nephropathy

			Singapore, Thailand, Taiwan					
Zoungas, S., et al [20]	2014	2001 – 2008	Australia Canada China Czech Republic Estonia France Germany Hungary India Ireland Italy Lithuania Malaysia Netherlands New Zealand Philippines Poland Russia Slovakia UK	11 140	65.8	42.5	Cohort	All-Cause Mortality Macrovascular Disease Microvascular Disease Coronary Heart Disease Cerebrovascular Vascular Disease Retinopathy Nephropathy

[a]*Numbers may vary slightly per outcome analysed, refer to the relevant meta-analysis NR= Not reported e=age at last examination*

[c] *The original publication provided results from 2005-2009 (n= 86 390). Odds Ratios in this meta-analyses are from updated data (unpublished) with results from 2005-2013 (n= 152 156)*

REFERENCES

[1] Rahelic D (2016) [7th Edition of Idf Diabetes Atlas--Call for Immediate Action]. Lijecnicki vjesnik 138: 57-58

[2] Song SH, Hardisty CA (2008) Early-onset Type 2 diabetes mellitus: an increasing phenomenon of elevated cardiovascular risk. Expert Rev Cardiovasc Ther 6: 315-322

[3] Sullivan MD, Anderson RT, Aron D, et al. (2007) Health-related quality of life and cost-effectiveness components of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial: rationale and design. The American journal of cardiology 99: 90i-102i

[4] Barr EL, Zimmet PZ, Welborn TA, et al. (2007) Risk of cardiovascular and all-cause mortality in individuals with diabetes mellitus, impaired fasting glucose, and impaired glucose tolerance: the Australian Diabetes, Obesity, and Lifestyle Study (AusDiab). Circulation 116: 151-157

[5] Gungor N, Bacha F, Saad R, Janosky J, Arslanian S (2005) Youth type 2 diabetes: insulin resistance, beta-cell failure, or both? Diabetes Care 28: 638-644

[6] Gungor N, Thompson T, Sutton-Tyrrell K, Janosky J, Arslanian S (2005) Early signs of cardiovascular disease in youth with obesity and type 2 diabetes. Diabetes Care 28: 1219-1221

[7] Song SH (2016) Early-onset type 2 diabetes: high lifetime risk for cardiovascular disease. The lancet Diabetes & endocrinology 4: 87-88

[8] Gungor N, Hannon T, Libman I, Bacha F, Arslanian S (2005) Type 2 diabetes mellitus in youth: the complete picture to date. Pediatric clinics of North America 52: 1579-1609

[9] Zou X, Zhou X, Ji L, et al. (2017) The characteristics of newly diagnosed adult early-onset diabetes: a population-based cross-sectional study. Scientific reports 7: 46534

[10] Ahlqvist E, Storm P, Karajamaki A, et al. (2018) Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables. The lancet Diabetes & endocrinology 6: 361-369

[11] Hillier TA, Pedula KL (2003) Complications in young adults with early-onset type 2 diabetes: losing the relative protection of youth. Diabetes care 26: 2999-3005

[12] Luk AO, Lau ES, So WY, et al. (2014) Prospective study on the incidences of cardiovascular-renal complications in Chinese patients with young-onset type 1 and type 2 diabetes. Diabetes care 37: 149-157

[13] Xu H, Aldrich MC, Chen Q, et al. (2015) Validating drug repurposing signals using electronic health records: a case study of metformin associated with reduced cancer mortality. J Am Med Inform Assoc 22: 179-191

[14] Cai X, Han X, Zhang S, Luo Y, Chen Y, Ji L (2014) Age at diagnosis and C-peptide level are associated with diabetic retinopathy in Chinese. PloS one 9: e91174

[15] Wong J, Molyneaux L, Constantino M, Twigg SM, Yue DK (2008) Timing is everything: age of onset influences long-term retinopathy risk in type 2 diabetes, independent of traditional risk factors. Diabetes Care 31: 1985-1990

[16] Ohno T, Kato N, Shimizu M, et al. (1993) Effect of age on the development or progression of albuminuria in non-insulin-dependent diabetes mellitus (NIDDM) without hypertension. Diabetes Res 22: 115-121

[17] Klein R, Klein BE, Moss SE, Cruickshanks KJ (1995) Ten-year incidence of gross proteinuria in people with diabetes. Diabetes 44: 916-923

[18] Mohan V, Vijayaprabha R, Rema M (1996) Vascular complications in long-term south Indian NIDDM of over 25 years' duration. Diabetes Res Clin Pract 31: 133-140

[19] Davis TM, Stratton IM, Fox CJ, Holman RR, Turner RC (1997) U.K. Prospective Diabetes Study 22. Effect of age at diagnosis on diabetic tissue damage during the first 6 years of NIDDM. Diabetes Care 20: 1435-1441

[20] Zoungas S, Woodward M, Li Q, et al. (2014) Impact of age, age at diagnosis and duration of diabetes on the risk of macrovascular and microvascular complications and death in type 2 diabetes. Diabetologia 57: 2465-2474
[21] Pavkov ME, Bennett PH, Knowler WC, Krakoff J, Sievers ML, Nelson RG (2006) Effect of youth-onset type 2 diabetes mellitus on incidence of end-stage renal disease and mortality in young and middle-aged Pima Indians. Jama 296: 421-426
[22] Yeap BB, McCaul KA, Flicker L, et al. (2015) Diabetes, myocardial infarction and stroke are distinct and duration-dependent predictors of subsequent cardiovascular events and all-cause mortality in older men. Journal of Clinical Endocrinology & Metabolism 100: 1038-1047
[23] Song SH, Hardisty CA (2009) Early onset type 2 diabetes mellitus: a harbinger for complications in later years--clinical observation from a secondary care cohort. QJM : monthly journal of the Association of Physicians 102: 799-806
[24] Yeung RO, Zhang Y, Luk A, et al. (2014) Metabolic profiles and treatment gaps in young-onset type 2 diabetes in Asia (the JADE programme): a cross-sectional study of a prospective cohort. The lancet Diabetes & endocrinology 2: 935-943
[25] Kenealy T, Elley CR, Robinson E, et al. (2008) An association between ethnicity and cardiovascular outcomes for people with Type 2 diabetes in New Zealand. Diabetic medicine : a journal of the British Diabetic Association 25: 1302-1308
[26] Stroup DF, Berlin JA, Morton SC, et al. (2000) Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. Jama 283: 2008-2012
[27] Moher D, Liberati A, Tetzlaff J, Altman DG, Group P (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA Statement. Open medicine : a peer-reviewed, independent, open-access journal 3: e123-130
[28] (Monash University and Monash Health M, Australia (2014) Monash Centre for Health Research and Implementation (MCHRI) Evidence Synthesis Program template for critical appraisal of a cohort study. In: (adapted from Critical Appraisal Templates (2010) Centre for Clinical Effectiveness SH, Melbourne, Australia (ed)
[29] Wells G SB, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. (2000) The Newcastle–Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. In: Proceedings of the 3rd Symposium on Systematic Reviews Beyond the Basics: Improving Quality and Impact. Oxford
[30] Centre TNC (2014) Review Manager (RevMan) In. The Cochrane Collaboration, Copenhagen
[31] DerSimonian R, Laird N (1986) Meta-analysis in clinical trials. Controlled clinical trials 7: 177-188
[32] Senn SS (2008) Statistical issues in drug development. John Wiley & Sons
[33] Higgins JP, Thompson SG (2002) Quantifying heterogeneity in a meta-analysis. Statistics in medicine 21: 1539-1558
[34] Egger M, Schneider M, Davey Smith G (1998) Spurious precision? Meta-analysis of observational studies. Bmj 316: 140-144
[35] Egger M, Davey Smith G, Schneider M, Minder C (1997) Bias in meta-analysis detected by a simple, graphical test. Bmj 315: 629-634
[36] Penno G, Solini A, Orsi E, et al. (2018) Non-albuminuric renal impairment is a strong predictor of mortality in individuals with type 2 diabetes: the Renal Insufficiency And Cardiovascular Events (RIACE) Italian multicentre study. Diabetologia 61: 2277-2289
[37] Huo X, Gao L, Guo L, et al. (2016) Risk of non-fatal cardiovascular diseases in early-onset versus late-onset type 2 diabetes in China: a cross-sectional study. The lancet Diabetes & endocrinology 4: 115-124
[38] Chan JC, Lau ES, Luk AO, et al. (2014) Premature mortality and comorbidities in young-onset diabetes: a 7-year prospective analysis. The American journal of medicine 127: 616-624

[39] Nanayakkara N, Ranasinha S, Gadowski A, et al. (2018) Age, age at diagnosis and diabetes duration are all associated with vascular complications in type 2 diabetes. Journal of diabetes and its complications 32: 279-290
[40] Pugliese G, Solini A, Zoppini G, et al. (2012) High prevalence of advanced retinopathy in patients with type 2 diabetes from the Renal Insufficiency And Cardiovascular Events (RIACE) Italian Multicenter Study. Diabetes Res Clin Pract 98: 329-337
[41] Amutha A, Anjana RM, Venkatesan U, et al. (2017) Incidence of complications in young-onset diabetes: Comparing type 2 with type 1 (the young diab study). Diabetes Res Clin Pract 123: 1-8
[42] Pradeepa R, Anjana RM, Unnikrishnan R, Ganesan A, Mohan V, Rema M (2010) Risk factors for microvascular complications of diabetes among South Indian subjects with type 2 diabetes--the Chennai Urban Rural Epidemiology Study (CURES) Eye Study-5. Diabetes technology & therapeutics 12: 755-761
[43] Amutha A, Datta M, Unnikrishnan IR, et al. (2011) Clinical profile of diabetes in the young seen between 1992 and 2009 at a specialist diabetes centre in south India. Primary care diabetes 5: 223-229
[44] Pradeepa R, Chella S, Surendar J, Indulekha K, Anjana RM, Mohan V (2014) Prevalence of peripheral vascular disease and its association with carotid intima-media thickness and arterial stiffness in type 2 diabetes: the Chennai urban rural epidemiology study (CURES 111). Diabetes & vascular disease research 11: 190-200
[45] Pradeepa R, Rema M, Vignesh J, Deepa M, Deepa R, Mohan V (2008) Prevalence and risk factors for diabetic neuropathy in an urban south Indian population: the Chennai Urban Rural Epidemiology Study (CURES-55). Diabetic medicine : a journal of the British Diabetic Association 25: 407-412
[46] Rema M, Premkumar S, Anitha B, Deepa R, Pradeepa R, Mohan V (2005) Prevalence of diabetic retinopathy in urban India: the Chennai Urban Rural Epidemiology Study (CURES) eye study, I. Investigative ophthalmology & visual science 46: 2328-2333
[47] Romero-Aroca P, Navarro-Gil R, Valls-Mateu A, Sagarra-Alamo R, Moreno-Ribas A, Soler N (2017) Differences in incidence of diabetic retinopathy between type 1 and 2 diabetes mellitus: a nine-year follow-up study. The British journal of ophthalmology 101: 1346-1351
[48] Song SH, Gray TA (2011) Early-onset type 2 diabetes: high risk for premature diabetic retinopathy. Diabetes Res Clin Pract 94: 207-211
[49] Thomas RL, Dunstan FD, Luzio SD, et al. (2015) Prevalence of diabetic retinopathy within a national diabetic retinopathy screening service. The British journal of ophthalmology 99: 64-68
[50] Unnikrishnan R, Anjana RM, Amutha A, et al. (2017) Younger-onset versus older-onset type 2 diabetes: Clinical profile and complications. Journal of diabetes and its complications 31: 971-975
[51] Unnikrishnan RI, Rema M, Pradeepa R, et al. (2007) Prevalence and risk factors of diabetic nephropathy in an urban South Indian population: the Chennai Urban Rural Epidemiology Study (CURES 45). Diabetes care 30: 2019-2024
[52] Huo L, Magliano DJ, Ranciere F, et al. (2018) Impact of age at diagnosis and duration of type 2 diabetes on mortality in Australia 1997-2011. Diabetologia 61: 1055-1063
[53] Chen MS, Kao CS, Chang CJ, et al. (1992) Prevalence and risk factors of diabetic retinopathy among noninsulin-dependent diabetic subjects. American journal of ophthalmology 114: 723-730
[54] Hamman RF, Mayer EJ, Moo-Young GA, Hildebrandt W, Marshall JA, Baxter J (1989) Prevalence and risk factors of diabetic retinopathy in non-Hispanic whites and Hispanics with NIDDM. San Luis Valley Diabetes Study. Diabetes 38: 1231-1237
[55] Yokoyama H, Okudaira M, Otani T, et al. (2000) Higher incidence of diabetic nephropathy in type 2 than in type 1 diabetes in early-onset diabetes in Japan. Kidney Int 58: 302-311
[56] Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA (2008) 10-year follow-up of intensive glucose control in type 2 diabetes. The New England journal of medicine 359: 1577-1589

[57] Group TS, Zeitler P, Hirst K, et al. (2012) A clinical trial to maintain glycemic control in youth with type 2 diabetes. The New England journal of medicine 366: 2247-2256
[58] Nanayakkara N, Pease AJ, Ranasinha S, et al. (2018) Younger people with Type 2 diabetes have poorer self-care practices compared with older people: results from the Australian National Diabetes Audit. Diabetic medicine : a journal of the British Diabetic Association 35: 1087-1095
[59] Kelley GA, Kelley KS, Tran ZV (2004) Retrieval of missing data for meta-analysis: a practical example. International journal of technology assessment in health care 20: 296-299

Figure Legends

Figure 1: Flow chart of systematic review

Figure 2: Effect of age at diagnosis (per 1 year increase), adjusted for current age on the risk of all-cause mortality, macrovascular and microvascular disease. The symbols are proportional to the study weight and horizontal lines represent 95% confidence intervals.

Figure 3: Effect of age at diagnosis (per 1 year increase), adjusted for current age on the risk of secondary outcomes. The symbols are proportional to the study weight and horizontal lines represent 95% confidence intervals. *For Unnikrishnan, R, Anjana RM., et al, older onset refers to those diagnosed aged >50 years and younger onset refers to those diagnosed aged ≤25 years